Return of the Vestibular Function Following Streptomycin Toxemia

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SUMMARY

Of 62 patients given 2 gm. of streptomycin daily for an average of 110 days, 42 had complete loss of vestibular response to caloric stimulation. In the great majority of cases, response returned in varying degrees over a period of two years. The incidence of loss of response was higher among patients who weighed less than 125 pounds than among heavier patients, and it was higher among patients over 45 years of age than among those who were younger. Response returned earlier in the younger patients than in the older.

Of 215 patients given 1 gm. of streptomycin for an average of 110 days, 18 had complete loss of vestibular response to stimulation. Sixteen regained response within a year, one in 17 months, and one was lost to study.

THIS report covers the vestibular reactions of 62 patients treated for pulmonary tuberculosis with 2 gm. of streptomycin daily, and 215 patients treated with 1 gm. of streptomycin daily, according to the Veterans Administration protocol.[15] (In 14 of the cases in which the larger dose was used, ulcerative tracheobronchitis was a complicating factor.) That streptomycin may cause defective hearing was not confirmed in investigations by Moffitt[11] and Davis[3] or in the Veterans Administration Streptomycin Conference Report.[13] The only exceptions were cases in which very large doses were given, or in cases of tuberculous meningitis.

All patients in the series here reported upon were examined for vestibular function before, during and after treatment.

Method of Examination: The modified Kobrak test of minimal stimulation was used, rather than the tilt table of Glorig,[5] or the nystagmograph of Linthicum.[9] The examinations were done by one examiner, thus reducing the variables in method and interpretation.

Five cubic centimeters of melted ice was instilled in the ear canal, with the head in a horizontal position, and the liquid was left there until nystagmus was observed with an ophthalmoscope, but not longer than a minute and a half. Nystagmus was considered normal if it started within 50 seconds and lasted from 60 to 90 seconds. The water was emptied out of the ear canal and the head put 60 degrees back, changing the direction of flow of the endolymph in relation to the canal. If the flow was normal, there was rotatory nystagmus.

McNally[10] stated that the whole body musculature is under the influence of the labyrinth and that the eye reactions are actually only a small part of the result of vestibular stimulation.

In the present series, past pointing tests were used to observe the effect of labyrinthine stimulation with regard to the loss or alteration of function in muscle groups other than those of the eyes.[1,6,7] With the head inclined 32 degrees forward and the eyes closed, the patient's arm was held outstretched before him and the index finger placed at a starting point. Then the arm, with the elbow straight, was swung upward until the hand was directly above the head. The patient then was directed to return the index finger to the starting point without bending the elbow. Pointing to the right after stimulation of the right ear and to the left after stimulation of the left ear was considered normal. Return of the index finger to the starting position indicated hypofunction of the labyrinth. If there was no nystagmus and the patient was unable even to approach the starting point in a past pointing test, he was considered to have complete loss of vestibular function.

After all results of stimulation had subsided, the ability to walk naturally on a level hard floor, with the eyes closed, was tested. Pronounced correlation between the amount of vestibular response and the ability to walk on a level hard floor was observed. When the vestibular response was reduced—that is, when there was a shortened duration of nystagmus, absence of rotatory nystagmus or diminished past pointing ability—the patient could take only a few steps with the eyes closed and then would start to fall. When there was no nystagmus or past pointing ability after caloric stimulation of each ear, the patient had difficulty in standing with the eyes closed and total inability to take even one step without falling. It is suggested that this walking test with the eyes closed may be used as a rough determination of the amount of vestibular function remaining.

The most disabling symptoms of streptomycin toxemia have been previously described as vertigo, dizziness and ataxia.[15,13,3,4,5,12] McNally[10] stated that dizziness and vertigo may result from stimula-

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tion, irritation or disease of any of the structures concerned in the maintenance of balance. There may be ocular vertigo, central vertigo or labyrinthine vertigo. Frequently, it is difficult to distinguish between the various causes.

Many patients with a decreased vestibular response have difficulty in walking, with their eyes open, on an inclined surface, on grass, or on a thick carpet and may require the assistance of another person. This difficulty is increased if the light is dim. They also complain of unsteadiness on turning quickly. When they suddenly sit up in bed or stand erect after stooping, the body seems to go too far and does not stop at the vertical position. In streptomycin toxemia there is nystagmus, lack of control of the head and trunk muscles, and difficulty in walking. It would seem, then, that the term "disturbance of equilibrium" would best describe the symptoms due to the neurotoxic effects of streptomycin.

Result of Examinations: All patients hereinafter reported had normal vestibular response in both ears before treatment with streptomycin. Of 62 patients who received 2 gm. of streptomycin daily for an average of 110 days, 89 per cent had a mild decrease in vestibular response at the end of six weeks. Thirty-two had complete loss of vestibular response during treatment, and ten more lost all response within two months after the treatment was discontinued. Of these 42, 14 regained some response during the first year (see Table 1), most of them in succeeding months regaining full normal caloric response with no disturbance of equilibrium.

TABLE 1.—*Data on Loss of Vestibular Response in 62 Patients Given 2 gm. of Streptomycin for 110 days.*

	During Prescription	Two Months After Prescription	Total
Positive*	20	20	20
Negative*	32	10	42

The 42 patients negative after prescription:

	End of First Year	Total Up to Second Year	Total Up to Third Year
Positive	14	26	28
Negative	25	5	3
Lost to study	3	8	8

*The term "positive" indicates no reduction or only partial reduction of vestibular response; "negative" means complete loss of response.

Of the 12 patients who regained some response during the second year, eight had a slight response in both ears and four had a slight response in only one ear after stimulation. All of these 12 were able to take from four to five steps with their eyes closed, walking on a level hard floor.

An interesting observation in these studies was how little vestibular response was necessary to enable patients to walk with their eyes closed, although equilibrium was not normal in every respect. Patients with hypofunction still had difficulty in walking in a dim light, in turning quickly, in riding in an automobile and in stepping down from a curbing, and vision of distant objects was blurred.

Return of Vestibular Function in Weight and Age Groups: The incidence of vestibular damage was higher among patients with body weight less than 125 pounds who received 2 gm. daily than it was among patients who were heavier than that. This conforms with Tompsett's[14] opinion regarding bodyweight dosage. There was lower incidence of loss of vestibular response in patients under 45 years of age than in patients in higher age brackets. In the younger group, vestibular response was regained earlier and complete recovery occurred much sooner than in the group over 45 years of age. Many of the older group who had some return of vestibular response still had pronounced disturbance of equilibrium for one or two years, and in a small percentage of these cases there was never a return to normal.

Peik and High[12] reported on 15 cases in which 2 gm. of streptomycin had been given daily. The toxic reactions were similar to those observed in this study. Four patients with moderate to severe loss of vestibular function recovered within seven to eleven months, two others showed slight improvement, one showed no response, all others continued to show serious to severe vestibular loss.

One Gram Dosage: Because of the frequent occurrence of the neurotoxic effect of streptomycin on the vestibular branch of the eighth nerve (which the preceding data show is not necessarily permanent) the Streptomycin Conference[13,15] changed its protocol to use 1 gm. of streptomycin rather than 2 gm. because of the early reports of the lessened toxicity with the use of the smaller dose.

Of 215 patients in the present series who were treated with 1 gm. for an average of 110 days, only 18 completely lost vestibular response to caloric stimulation in both ears. All but two regained some response within the first year. One more regained some response 17 months after discontinuance of the drug and one was lost to study (see Table 2).

TABLE 2.—*Studies of 215 Patients Receiving 1 gm. of Streptomycin for 110 Days*

	After Treatment	End of First Year	End of Second Year
Positive	197	213	214
Negative	18	2	0
Lost to study	....	0	1

The recovery of equilibrium following loss or hypofunction due to the treatment with 1 gm. was much more rapid than recovery after loss of equilibrium under 2 gm. dosage.

As a certain amount of compensation was acquired by patients with hypofunction, walking and turning were a little more steady as time went on. It is probable that this improvement in equilibrium

was due more to gradual return of vestibular function in one or both ears than to the patient's learning to get along without complete labyrinthine control of equilibrium. Bauer[1] stated that the chief factors concerned in the maintenance of equilibrium are vision, the vestibular mechanism, and deep muscle sense, including sensations from the bones, joints and tendons.

Location of Lesion: Winston and Lewey,[16,17] using phospho-tungstic acid and cresylviolet, demonstrated pyknosis and increase of glial fibers around the dendrites of the Purkinje cells in the cerebellum of cats treated with large doses of streptomycin. Jones[6] reported a case of localized encephalitis in which there was no loss of hearing in either ear but complete loss of all vestibular response to both whirling chair and caloric stimulation, ten days before death. In microscopic examination of serial sections of the brain, a localized area of complete degeneration was observed in the center of the tegmentum, extending from the lower part of the medulla oblongata well into the lower part of the pons, with the raphe as its center. It may be concluded that nearly all of the central tracts concerned with vestibular function pass through the area represented by this degeneration, and that few of the fibers of the cochlear system are represented in this region. Fowler,[4] early in the research, reported no abnormal findings at autopsy in sections of the internal ear of patients treated with streptomycin.

Winston and Lewey[17] recently reported that by the vital staining technique, pathologic changes were observed in the cerebellum and medulla in 50 per cent of cats that had been given streptomycin in three divided daily doses. No pathologic changes were detected by this method in cats that had received streptomycin in one daily injection. Of the cats in which pathologic changes were noted, nearly all had lesions in the vestibular portion of the cerebellum; one-third of them changes in the cochlear system, and one-sixth in the vestibular nuclei of the brain stem.

With regard to vertigo caused by certain drugs, Lindsay[8] stated that the occurrence of dizziness and nystagmus in connection with change in the position of the head (which changes the direction of the flow of endolymph) is a fairly reliable indicator of a centrally located lesion.

Berg,[2] on the other hand, concluded that streptomycin primarily affects the sensory epithelium of the labyrinth, and he expressed the belief that the changes in the vestibular ganglion and in Deiters' nucleus presumably are secondary to the primary lesion of the sensory epithelium.

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